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ORIGINAL ARTICLE

Glucose, insulin, and insulin resistance in normal-weight, overweight and obese children with obstructive sleep apnea

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KEYWORDS
Sleep apnea;
Obesity;
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Summary
Background: Obstructive sleep apnea (OSA) is associated with components of metabolic syndrome. Both body weight and OSA independently influence metabolic measurements. The goal of this study was to determine whether OSA in normal-weight, overweight or obese children, compared to matched control groups, was associated with increased levels of glucose, insulin and insulin resistance (IR).
Methods: Age- and gender-specific body mass index (BMI) percentiles were determined and used to categorize subjects into normal-weight (BMI < 85%) and overweight-obese (BMI ≥ 85%) groups. In addition, subjects were divided into normal-weight (BMI < 85%), overweight (BMI ≥ 85% and <95%) and obese (BMI ≥ 95%) groups. Polysomnography was conducted and morning levels of glucose and insulin were measured and IR was determined from the blood samples collected early in the morning after overnight fast. Results were compared between the subject groups. Effects of severity of OSA defined by apnea hypopnea index (AHI) and oxygen desaturation index (ODI) on glucose, insulin, and HOMA-IR were analyzed.
Results: Glucose, insulin, and HOMA-IR in OSA and matched control groups were not significantly different for normal-weight, overweight and obese subjects. The ODI was significantly associated with elevated levels of glucose and HOMA-IR after adjustment for age, gender, race, and BMI *Z*-score.
Conclusions: IR levels between OSA and control for both normal-weight, overweight and obese subjects were not significantly different. The ODI was associated with

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increased IR in children with OSA. OSA-induced hypoxic events during sleep may be a potential mechanism of increased IR in children with OSA, independent of body weight.

Introduction

Obstructive sleep apnea (OSA) in children has been linked to metabolic syndrome [1]. Insulin resistance (IR) is an important component of metabolic syndrome that is elevated in patients with OSA, independent of obesity [2]. However, studies using the homeostasis model assessment model (HOMA) for IR measurements in children with OSA have produced conflicting results, with both increased [3,4] and similar [5,6] HOMA-determined IR (HOMA-IR) in OSA and control subjects. Although a causal association between OSA and metabolic syndrome is yet to be established, obesity is the common co-morbidity associated with both OSA and metabolic syndrome [7]. Also, obesity and OSA are independently associated with all of the parameters of metabolic syndrome, including increased blood pressure [8], hyperglycemia [9], hyperinsulinemia [3], increased IR [10], diabetes mellitus [11], and increased triglyceride levels [12,13], as well as prothrombotic [14] and proinflammatory [15] conditions. Recent data suggest significant improvements of metabolic dysfunction after nasal continuous positive airway pressure treatment of OSA [16]. Although obesity is a major risk factor for OSA in both adults [17,18] and children [19,20], limited data are available comparing the effects of OSA on metabolic measurements in either normal-weight or obese children. For this study, we assessed levels of plasma glucose and insulin, as well as HOMA-IR, in normal-weight and overweight children with or without OSA to determine whether children with OSA have weight-dependent increases in these metabolic syndrome components compared to respective control groups matched for age, gender, and race. In addition, we determined the effects of severity of OSA, as evidenced by levels of apnea hypopnea index (AHI) and oxygen desaturation index (ODI) during sleep, on both glucose and insulin levels and HOMA-IR.

Methods

Subjects

Children between 5 and 14 years of age were recruited from the Otolaryngology and Pediatric Clinic of Cincinnati Children's Hospital Medical Center (CCHMC) for an overnight sleep study using polysomnography (PSG) for diagnosis of OSA. Height and body weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. Age- and gender-specific *Z*-scores (measurement of a score's relationship to the mean in a group of scores) for body mass index (BMI) were calculated using reference data available in the Centers for Disease Control and Prevention 2000 growth charts for the United States [21]. Children with OSA were divided by BMI percentile into overweight (BMI $\geq$ 85%) and normal-weight (BMI < 85%) groups. In addition, subjects were divided into normal-weight (BMI < 85%), overweight (BMI $\geq$ 85% and <95%) and obese (BMI $\geq$ 95%) groups. Healthy children matched for age, gender, race, and BMI percentile also were recruited for PSG as control subjects for the OSA groups. The OSA subjects were free of cardiovascular, cerebrovascular, and other chronic medical disorders or genetic conditions, had never been treated for OSA, and were on no medications. The control subjects were free of any acute or chronic disease and were on no medications, and those with snoring, occult OSA (AHI $\geq$ 1 event/h), and alveolar hypoventilation on PSG were excluded from the study. Parental-signed informed consent for all children and assent for children over 7 years of age were obtained from each study participant prior to enrollment into the study. The study was approved by the CCHMC Institutional Human Subjects Review Board.

Study design

A medical history was obtained and a physical examination was performed on all subjects before the sleep study. Parents remained with their children throughout the night. Children were neither deprived of sleep prior to the study nor given sedatives. Demographic data was determined and heart rate and blood pressure were measured for each subject prior to the sleep study. Venous blood was collected in the early morning, between 6:00 am and 7:00 am, after overnight fasting for measurements of glucose and insulin. The presence

and severity of OSA were determined by standard overnight PSG.

Polysomnography: PSG was conducted using a computerized system (Grass, Telefactor, Astro Inc., Westwarwick, RI). Recording variables were electroencephalogram (C_3-A_2, C_4-A_1, O_1-A_2, and O_2-A_1); right and left electrooculogram (EOG); submental, tibial, and intercostal electromyogra (EMG); electrocardiography (ECG); nasal/oral airflow through nasal pressure sensor; end-tidal CO_2 measured at the nose by infrared capnometry using the Nelcor N1000 (Van Nuys, CA); oxygen saturation by pulse oximeter (Nelcor N1000); and rib cage and abdominal volume changes with a computer-assisted respiratory inductance plethysmograph (Somnostar, Noninvasive Monitoring System Inc., Miami Beach, FL). Sleep staging was performed according to the rules of Rechtschaffen and Kales [22]. All sleep studies were scored, according to the standard criteria set by the American Academy of Sleep Medicine [23], by the same board-certified sleep specialist (RSA). Results obtained from the polysomnography were sleep duration, percentage of sleep time spent in different stages of sleep; number of arousals from sleep; and AHI, ODI, oxygen saturation index, number of episodes of oxygen desaturation by 4% or more per hour of sleep.

Glucose analysis: The quantitative determination of glucose was performed using the Roche Cobas C311 chemistry analyzer (Roche Diagnostics, Indianapolis, IN, USA). Blood samples were treated with glucose oxidase to form gluconate and hydrogen peroxide, and then phenol and 4-aminoantipyrine was added in the presence of peroxidase to produce a quinoneimine dye that was measured at 500 nm absorbance, which was proportional to the concentration of glucose in the sample. Low-control, within-assay coefficient of variation (CV) was 0.66% and between-assay CV was 1.63%. High-control, within-assay CV was 0.49% and between-assay CV was 1.56%. The normal range of glucose was 65—115 mg/dl.

Insulin analysis: Fasting insulin levels were determined by a radioimmunoassay. To develop a standard curve, a fixed concentration of labeled tracer antigen was incubated with a constant dilution of antiserum. Since unlabeled antigen competes for a limited and constant number of binding sites on the antibody, the amount of tracer bound to antibody was decreased as the concentration of unlabeled antigen increased. After phase separation with a precipitation reagent was completed, the resulting pellet was counted using a Packard gamma counter (Ramsey, MN, USA). Each standard curve was configured with increasing, known concentrations of standard, unlabeled antigen and used to calculate the amount of antigen in each unknown sample. The Linco Research Human Insulin assay (Linco Research, St Charles, MO, USA) utilizes ^{125}I-labeled human insulin and a human insulin antiserum to determine the level of insulin in plasma using the double-antibody/PEG technique. Low-control within-assay CV was 3.1% and between-assay CV was 12.6%. High-control within-assay CV was 4.4% and between-assay CV was 5.3%. The normal range of insulin was 5—15 μU/ml.

Calculation of IR: HOMA-IR was calculated from the fasting glucose and insulin levels where the product of fasting glucose in mg/dl and fasting insulin in μU/ml was divided by 405.

Statistical analysis

A descriptive analysis was performed with calculation of means, standard deviations, and medians for continuous variables and proportions for categorical variables. Demographic variables were compared between groups using Wilcoxon rank sum tests for continuous variables and likelihood-ratio chi-square tests for categorical variables. Bivariate associations of continuous variables of sleep, glucose, and insulin were analyzed using Spearman correlation coefficients. An analysis of covariance (ANCOVA) model was used to compare groups for differences in insulin and glucose levels and HOMA-IR. Age, gender, and race were included as covariates. Least-square means were compared between groups of interest, with a simulated adjustment for multiple comparisons. Significance was set a priori at $\alpha = 0.05$. Analyses were performed using SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

Glucose, insulin, and HOMA-IR in normal-weight children with and without OSA

Normal-weight OSA and normal-weight control subjects were similar with regard to age, gender, race, BMI, and BMI *Z*-score (Table 1). Systolic, diastolic, and mean BP was not different between normal-weight children with or without OSA. Total sleep time, sleep efficiency, sleep latency, and rapid eye movement (REM) sleep latency were similar in the normal-weight OSA and control groups. Percent of sleep stages for Stage 2 and slow-wave sleep also were not different in these groups. However, there were statistically significant differences in Stage 1 and REM sleep between the normal-weight

Table 1 Characteristics and sleep profile of the study population.

	Normal-weight control ($N = 56$)	Normal-weight OSA ($N = 51$)	Overweight control ($N = 38$)	Overweight OSA ($N = 60$)
Gender, female:male	29:27	29:22	19:19	40:20
Age, years	9.4 ± 2.7	8.7 ± 2.9	$10.9 \pm 2.3^{\$}$	$9.8 \pm 2.4^{\#,¥}$
Race, Caucasian:others	36:20	31:20	22:16	29:31
BMI, kg/m^2	17.2 ± 2.0	17.8 ± 6.6	$24.9 \pm 4.7^{\$}$	$25.8 \pm 10.8^{¥}$
BMI *Z*-score	0.2 ± 0.6	0.1 ± 0.8	$1.7 \pm 0.4^{\$}$	$1.9 \pm 0.4^{¥}$
Systolic BP, mm Hg	104 ± 10	104 ± 8	$112 \pm 10^{\$}$	$111 \pm 10^{¥}$
Diastolic BP, mm Hg	60 ± 6	59 ± 5	$63 \pm 7^{\$}$	$62 \pm 6^{¥}$
Mean BP, mm Hg	75 ± 8	74 ± 7	$80 \pm 8^{\$}$	$79 \pm 8^{¥}$
Total sleep time, min	524 ± 40	536 ± 42	532 ± 33	530 ± 40
Sleep efficiency, %	80 ± 12	78 ± 11	80 ± 12	77 ± 12
Sleep latency, min	56 ± 49	62 ± 44	47 ± 37	58 ± 45
REM latency, min	183 ± 73	176 ± 66	154 ± 61	179 ± 72
Stage 1 sleep, %	3.2 ± 1.6	$2.5 \pm 1.1^{*}$	2.8 ± 1.4	2.8 ± 1.2
Stage 2 sleep, %	46 ± 8	46 ± 8	48 ± 8	48 ± 6
Slow-wave sleep, %	30 ± 7	30 ± 7	26 ± 7	29 ± 5
REM sleep, %	20 ± 5	$22 \pm 5^{*}$	21 ± 4	$20 \pm 4^{¥}$
AI, events/h	10.5 ± 2.9	12.3 ± 5.6	8.0 ± 2.3	$13.9 \pm 9.0^{\#}$
RDI, events/h	1.0 ± 1.4	$7.7 \pm 8.1^{*}$	0.6 ± 0.4	$8 \pm 7.6^{\#}$
AHI, events/h	0.3 ± 0.3	$7.0 \pm 8.2^{*}$	0.4 ± 0.3	$7.5 \pm 7.7^{\#}$
REM sleep SpO_2, %	98 ± 2	97 ± 1	98 ± 1	98 ± 1
Non-REM SpO_2, %	97 ± 1	97 ± 1	97 ± 1	97 ± 1
ODI, events/h	2.7 ± 2.3	$5.3 \pm 4.1^{*}$	3.4 ± 2.8	$8.8 \pm 8.5^{\#}$

BMI, body mass index; AI, arousal index; RDI, respiratory disturbance index; AHI, apnea hypopnea index; SpO_2, oxygen saturation; ODI, oxygen desaturation index during sleep. Values are means $\pm$ SD.

* $P < 0.05$, normal-weight control vs. normal-weight OSA.

# $P < 0.05$, overweight control vs. overweight OSA.

$ $P < 0.05$, normal-weight control vs. overweight control.

¥ $P < 0.05$, normal-weight OSA vs. overweight OSA.

OSA and control groups. Arousal index (AI) and levels of mean oxygen saturation during REM and non-REM sleep and lowest oxygen desaturation during sleep were not different in normal-weight OSA and control subjects. However, the normal-weight OSA subjects had significantly higher AHI, respiratory disturbance index (RDI), and ODI compared to normal-weight control subjects. Glucose, insulin, and estimated HOMA-IR after adjustment for age, gender, and race were not significantly different in both groups.

Glucose, insulin, and HOMA-IR in overweight subjects with and without OSA

Overweight OSA and overweight control subjects were similar with regard to gender, race, BMI, and BMI *Z*-score (Table 1). Systolic, diastolic, and mean BP was not different between overweight subjects with and without OSA. However, the overweight children had significantly increased systolic, diastolic, and mean BP compared to normal-weight children for both control and OSA subject groups. Sleep profile and mean oxygen saturation during REM and non-REM sleep were not different in overweight OSA or control subjects. AI, RDI, AHI, and ODI in overweight OSA subjects were significantly increased compared to overweight control subjects. Estimated glucose, insulin, and HOMA-IR, after adjustment for age, gender, and race, were not significantly different in both groups.

Effects of severity of OSA on HOMA-IR

Relationships between HOMA-IR and either AHI or ODI are shown in Fig. 1. Levels of AHI during sleep were not associated with HOMA-IR after adjustment for age, gender, race, and BMI *Z*-score. Levels of ODI during sleep were significantly ($P < 0.05$) and positively associated with increased HOMA-IR after adjustment of the covariates. However, HOMA-IR and ODI relationships were not significantly different between normal-weight and overweight subjects.

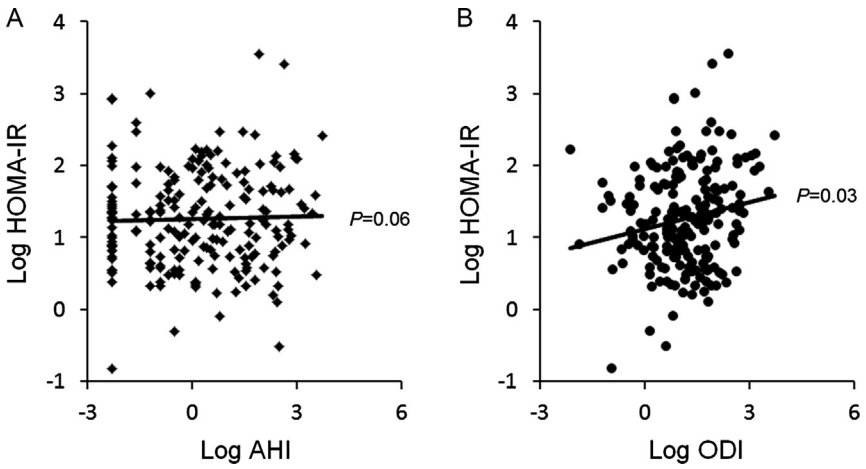

Figure 1 Relationship between log transformed HOMA-IR and log transformed AHI (A) and between log transformed HOMA-IR and log transformed oxygen desaturation index (ODI) (B). HOMA-IR is significantly associated with ODI ($P = 0.03$).

Effects of obesity on glucose, insulin, and HOMA-IR in OSA and control subjects

Overweight control subjects had significantly higher insulin and HOMA-IR compared to normal-weight control subjects after adjustment for age, gender, and race (Fig. 2A). Levels of glucose, insulin, and HOMA-IR were significantly higher in overweight OSA compared to normal-weight OSA subjects after adjustment for age, gender, and race (Fig. 2B). In addition, there were no significant differences in glucose, insulin, and HOMA-IR between OSA and control in normal-weight, overweight, or obese subjects. Obese subjects had significantly increased

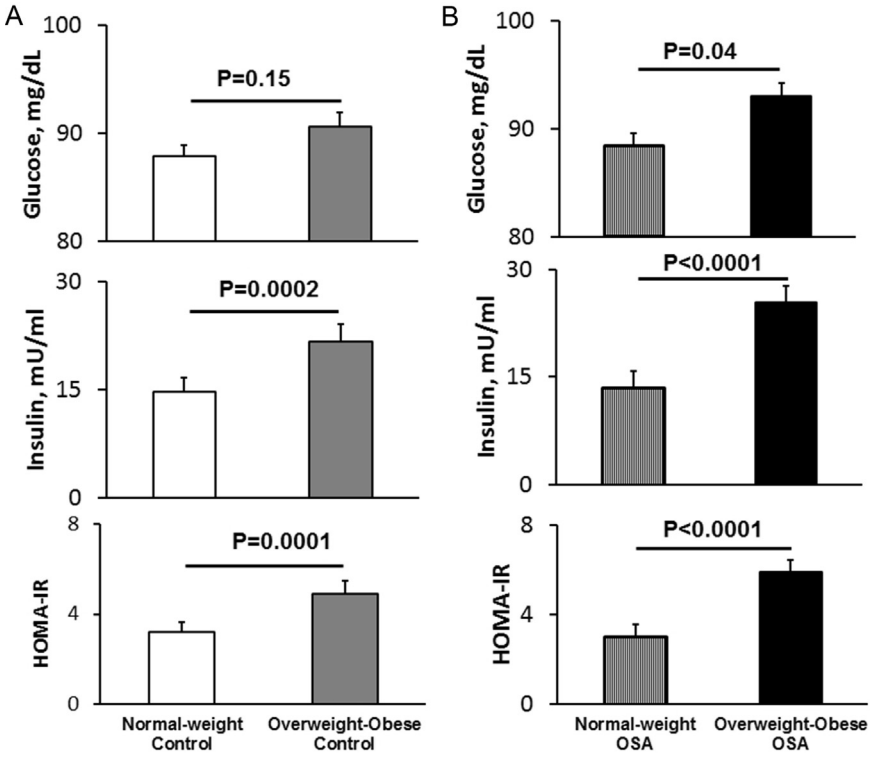

Figure 2 Glucose, insulin, and HOMA-IR in normal-weight control and overweight-obese control subjects (A) and in normal-weight OSA and overweight-obese OSA subjects (B). Overweight-obese subjects in both OSA and control groups have significantly increased insulin and HOMA-IR compared to normal-weight subjects.

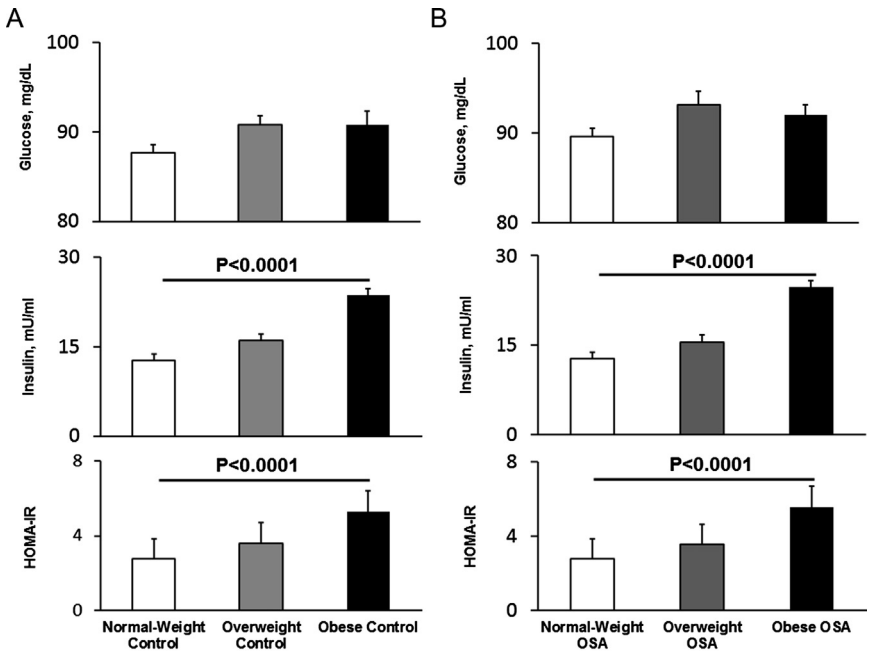

Figure 3 Glucose, insulin, and HOMA-IR in normal-weight, overweight and obese control subjects (A) and in normal-weight, overweight and obese OSA subjects (B). Obese subjects have significantly increased insulin and HOMA-IR compared to normal-weight subjects.

glucose, insulin, and HOMA-IR compared to normal-weight subjects for both the OSA and control groups (Fig. 3).

Discussion

Insulin and HOMA-IR were significantly elevated in overweight and obese subjects compared to normal-weight subjects for both OSA and control groups. However, the levels were not significantly different between the OSA and control subjects for either normal-weight or overweight-obese groups. The most intriguing result of our study was that severity of OSA, as defined by ODI, was associated with increased IR. In contrast, neither the presence nor severity of OSA, as defined by AHI during sleep, had any effect on HOMA-IR. Our findings suggest that hypoxic events during sleep are associated with increased levels of IR in the early morning in both normal-weight and overweight children with OSA.

Intermittent nocturnal hypoxemia is an important mechanism for increased sympathetic activity [24], metabolic [25] and proinflammatory cytokines [26], and cardiovascular mortality [27]. Elevated sympathetic tone may be a mechanism of increased IR [28]. Both animal [29] and human [30] studies of the effects of intermittent hypoxia on IR have suggested a causal association between hypoxia and IR. Severity of hypoxia in the children with OSA in our study was associated with increased levels of morning glucose, insulin, and HOMA-IR (Fig. 1). Sleep fragmentation due to repeated nighttime arousals from sleep also have been considered as a mechanism of sympathetic neurohumoral activation [31], and metabolic dysfunction [32], and consequently cardiovascular dysfunction in patients with OSA. Therefore, increased AI in children with OSA, particularly those that are overweight (Table 1), may play an important role in the increase in glucose, insulin, and HOMA-IR that we observed during early-morning hours.

Age, gender [33], race [34], and puberty [35] in children also affect insulin level and IR. Our case-control study strictly followed predetermined criteria for selection of subjects. Overweight and normal-weight OSA subjects were matched for age, gender, race, and BMI *Z*-score to their respective control groups. Therefore, average age, gender, and race were similar in subjects with OSA and controls, for both overweight and normal-weight groups. The major limitation of our study was that the pubertal status of subjects was not determined. However, it might be expected that since the ages of the children were similar, the numbers of children who had entered puberty would be similar between the groups. Also, the findings of our study were adjusted for age, gender, and race. Therefore, significant effects of ODI on

HOMA-IR likely were not related to age, gender, or race.

Obesity is an established risk factor for OSA in both adults [36,37] and children [19,7]. Abdominal and visceral obesity in particular is a major component of metabolic syndrome [38] and an independent predictor of OSA [39]. Visceral obesity also is significantly associated with IR [39]. For our study, the children with OSA were divided into overweight and normal-weight groups according to BMI percentile (overweight, BMI $\geq$ 85% and normal-weight, BMI < 85%). The BMI *Z*-scores that were determined measure the degree of adiposity and correlated well with direct measures of body fat. However, this measure does not differentiate visceral and peripheral adiposity. All four subject groups, OSA and control, both normal-weight and overweight, were similar regarding demographics and sleep profile, except for specific measures of OSA such as AI, RDI, and AHI (Table 1). The HOMA-IR results we obtained support results of previous studies regarding similar findings of insulin levels and IR in normal-weight OSA and control subjects [5,6]. One previous study reported a significant increase in IR in children with OSA who also were overweight or obese [6]. In our study, although overweight OSA subjects did have increased levels of glucose, insulin, and HOMA-IR (Fig. 2), the levels were not significant compared to matched overweight control subjects. In addition, glucose, insulin, and HOMA-IR also were compared between OSA and control subjects in normal-weight, overweight, and obese groups. Although obese subjects had significantly increased glucose, insulin, and HOMA-IR compared to normal-weight subjects (Fig. 3), the differences between OSA and matched control were not significant. Thus, levels of HOMA-IR were not significantly different in obese subjects with OSA compared to obese subjects without OSA. Our results showed that the severity of hypoxic events during sleep was significantly associated with increased levels of IR after adjustment of BMI *Z*-scores (Fig. 1). Thus, hypoxia during sleep may be a potential mechanism of abnormal glucose metabolism in children with OSA.

In conclusion, HOMA-IR levels in normal-weight, overweight, and obese children with OSA were not significantly different compared to respective matched control subjects because the presence of OSA defined by the level of AHI was not associated with increased HOMA-IR. However, nighttime hypoxic events during sleep were associated with increased HOMA-IR in both normal-weight and overweight subjects with OSA. Thus, nighttime hypoxemia in children with OSA may be a potential mechanism of increased IR in OSA that is independent of body weight. Therefore, treatment of OSA with adenotonsillectomy may eliminate nighttime hypoxic stress and improve IR. Our future studies will address the effects of adenotonsillectomy on IR in both normal-weight, overweight, and obese children with OSA.

Conflict of interest

No conflict of interest for all authors.

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